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The Role of Salt in Hypertension

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There is considerable evidence that salt is an important cause of hypertension. Primitive societies who ingest little or no salt have no hypertension. Also when diets very low in salt such as the rice and fruit diet are given to hypertensive patients, the blood pressure often falls toward normal. Unfortunately, when diets only moderately low in sodium have been given only minor reductions in blood pressure occur. Salt-induced hypertension has been produced in both man and experimental animals. The basic cause of the hypertension is an inability of the kidney to excrete the increased salt. Hemodynamic changes then occur which raise the blood pressure and so excrete the excess salt by pressure diuresis. The ability to excrete salt at normal levels of blood pressure varies from one individual to another. Those who require a higher than normal blood pressure are said to be "salt-sensitive". Those who can excrete excess salt at normal levels of blood pressure are called "salt resistant". The difference may be due to an inherited defect in the kidney to excrete salt. In any event, salt sensitive hypertension is effectively controlled with the administration of diuretics. *Key words: salt hypertension, hypertension, sodium in hypertension, high blood pressure and salt.*

INTRODUCTION

The importance of salt in hypertension has been emphasized for many years, first by Ambard & Beaujard [1] in 1904 and later by Allen [2], Meneely [3] and Dahl [4]. There is considerable evidence to support the hypothesis that essential hypertension frequently is the result of ingestion of salt. The continual use of salt as a condiment is not natural to man who in the primitive state consumed very little of it. The consumption of salt which modern man regards as normal is a comparatively recent development and may, in fact, be far greater than his biology is adapted to sustain. A possible mechanism by which salt may exert a hypertensive effect involves the following observations.

EVIDENCE FROM UNACCULTURATED SOCIETIES

Recent studies of unacculturated societies have disclosed that cultures who have practically no contact with the rest of the world and who live under primitive conditions have little or no hypertension. Another characteristic of these peoples, which is opposite to ourselves, is that the blood pressure does not rise with age. These characteristics have been noted among unacculturated peoples in such widely separated parts of the world as Africa [5] the South Pacific [6] the highlands of Malaysia [7] and the Amazon Basin of South America [8].

In searching for differences in habits that might account for the absence of hypertension among primitive peoples investigators have noted a common thread which was characteristic of the life style of these peoples and not of ours. Lowenstein [8] surveyed two neighboring tribes that lived in the Amazon basin. One of these tribes, the Manducuras, had been converted by the missionaries who also introduced them to the use of table salt. Although still living under relatively primitive conditions these people exhibited a rise of blood pressure with age and hypertension. The Carajas, on the other hand, who were not converted and did not use salt, exhibited no rise of blood pressure with age and no hypertension.

Additional evidence was provided by Prior et al. [9]. They measured blood pressure and estimated salt intake (from both dietary histories and 24 h urine collections) in two ethnically similar but culturally different tribes of Polynesians, the relatively acculturated Raratongans and the less acculturated Pukapukans. Among the former, sodium intake averaged 125 mEq per day and hypertension was common. Among the Pukapukans the sodium intake was much lower and hypertension was rare.

Page et al. [10] investigated 6 different societies in the Solomon Island. Some were quite acculturated while others were not. In agreement with Prior they found the lowest incidence of hypertension and the smallest intake of salt in the more unacculturated societies while those who adapted our ways had a high ingestion of salt, a rise of blood pressure with age and a high incidence of hypertension.

The most extensive and most striking observations were made on the Yanomamo Indians of Brazil [11]. The salt consumption of these people was extremely low and the average sodium excretion in the urine was only 1 mEq per day. Blood pressure did not rise with age and hypertension was completely absent. Other interesting observations were made. Plasma renin activity and

aldosterone excretion rates were markedly elevated by our standards of normality despite the complete absence of vascular disease. Undoubtedly these high values were a reflection of the extremely low salt intake which, in turn, activated the sodium conserving mechanisms. In addition to being essentially salt-free the diet also was high in potassium. Whether this contributed to their freedom from hypertension is not known.

On the basis of these and other similar observations there is at least an association between lack of hypertension in unacculturated peoples and the fact that salt is not added to their diet. By contrast, it should be noted that salt ingestion is extremely high in our culture. Not only is it added in cooking and at the table but it is also used as a flavoring agent in almost all prepared foods even including bread. The average salt consumption in most parts of the world is about 10 g per day and in some areas such as in northeast Japan, it rises to 20 to 30 g per day. In the primitive societies where hypertension is completely absent the salt intake is less than 0.1 g per day, a hundred-fold difference from our average intake. We have departed a long way from the salt intake of our primitive forebears and it would not be surprising if this was a stress that some of us are not able to cope with, particularly as we grow older.

THE ROLE OF SALT IN EXPERIMENTAL HYPERTENSION

How could salt exert a hypertensinogenic effect? Sodium is retained predominately extracellularly in contrast to potassium which is almost entirely intracellular. Excessive salt ingestion is associated with excessive thirst because of the body's need to maintain the isotonicity of extracellular fluid. Cattlemen in the old days increased the weight of these animals prior to marketing by feeding them excess salt and then allowing them free access to water. If expansion of extracellular fluid goes too far, however, edema will result against which the body has defenses. It is precisely these defense reactions which may provide the basis for hypertension. In order to clarify this concept it is necessary to review some of the studies on experimental hypertension.

The initial observations were made by Ledingham [12] who studied Goldblatt hypertension in rats subjected to renal artery constriction. He made the important observation that prior to the development of the elevated blood pressure there was an increase in extracellular volume. This observation caused Ledingham to investigate the cardiac output changes in rats during the development of renal vascular hypertension [13]. He found that the early rise in extracellular volume was associated with an increase in cardiac output and this, in turn, led to an increase in blood pressure. When the blood pressure rose the elevated extracellular volume was prevented from rising further because of pressure diuresis. With the further passage of time there was an increase in total peripheral resistance and a fall in cardiac output back to preoperative levels.

Ledingham postulated that the chain of events leading to hypertension originated with the initial expansion of extracellular volume and then progressed as follows: (*i*) extracellular volume is in equilibrium with plasma volume and expansion of the former leads to an increase in the latter. (*ii*) A rise in plasma volume and of tissue pressure increases venous pressure and venous return to the heart. (*iii*) By Starling's law of the heart an increase in venous return and right heart filling pressure causes a rise in cardiac output. (*iv*) If cardiac output rises and total peripheral resistance does not fall proportionately blood pressure will rise. (*v*) This elevation of blood pressure raises the glomerular filtration rate and produces diuresis thereby preventing further expansion of the extracellular volume. (*vi*) Because cardiac output is increased above normal the tissues will receive more blood supply than they need. The microcirculation responds to such an excess blood supply by vasoconstriction thereby raising total peripheral resistance. (*vii*) The increased resistance reacts on the left ventricle to reduce the cardiac output back toward normal. (*viii*) The final hemodynamic state, therefore, resembles that seen in human essential hypertension which is characterized by an elevated total peripheral resistance and an essentially normal cardiac output.

Ledingham's work received little attention at the time it was first published. However, it has received confirmation by other investigators using different methods for expanding the extracellular volume. Borst [14] was a clinician in Holland, a country in which the eating of licorice is popular. Licorice contains a substance which has an action similar to mineralocorticoid and is known to cause sodium retention and hypertension when ingested in large amounts. Borst studied the hemodynamic changes leading to the hypertension in volunteers fed excess licorice. They exhibited a rise of blood pressure which was initially associated with an elevation in cardiac output. Borst postulated an unknown renal defect requiring a higher than normal blood pressure to excrete the increased salt and water load.

A direct relationship between arterial blood pressure and urine volume was first shown by Selkurt [15]. Perfusing the isolated kidney at different arterial pressures he demonstrated a direct relationship between perfusion pressure and urine volume. This is an important piece in the puzzle of salt and hypertension because it provides a positive feedback mechanism for getting rid of a chronic excess of extracellular volume. Apparently, our regulatory mechanism prefers developing

hypertension to developing edema. However, nature did not anticipate that the excess salt and water load would be continuous as is the case with modern man.

Arthur Guyton used a more direct approach to induce a continuous expansion of extracellular volume [16]. In dogs he removed one kidney and half of the other and then loaded the animals with saline solution. He noted the same sequence of hemodynamic events, i.e. initial high output hypertension followed by high resistance hypertension which had been described by Ledingham. Guyton also constructed computed flow diagrams to demonstrate the various inter-relationships of different feedback loops involved in the regulation of blood pressure. He concluded that the common denominator in the development of any chronic elevation of blood pressure is the need for the kidney to increase urine volume and sodium excretion. Guyton postulated that the intrinsic functional capacity of the kidney to excrete salt and water varies from one individual to another. Those with a restricted functional capacity retain the salt and water, which results in hypertension ("salt-sensitive hypertension"). The hypertension in turn permits the kidney with reduced functional capacity to excrete the excess salt and water load. Homeostasis between salt ingestion and salt excretion is established at the expense of an increased blood pressure.

EVIDENCE FOR A RENAL DEFECT IN HANDLING SALT

Neither Guyton nor anyone else has as yet been able to identify a specific renal defect in early essential hypertension. However, there is now evidence indicating that the kidneys in spontaneously hypertensive rats do have intrinsic hypertensinogenic properties and fail to excrete salt and water loads efficiently.

The first piece of evidence comes from cross-transplantation experiments. Bianchi [17] transplanted the kidneys of a salt sensitive hypertension-prone strain of rats into normal rats. Hypertension developed in the normal rats with kidneys taken from the hypertension prone animals. Then he transplanted the kidneys from normal rats into hypertensive animals. Blood pressure normalized in the latter. Working independently precisely similar observations were made by Dahl [18] thus confirming the important observation that the kidneys seem to be the locus of the hypertension in this type of inherited rat hypertension.

What is the nature of this renal defect? Could it be associated with the ability of the kidney to excrete salt and water? Tobian indicated that this is the case [19]. He repeated Selkurt's isolated kidney perfusion experiments, only he compared kidneys from hypertension-resistant and hypertension-prone strains of rats. He found that a higher arterial perfusion pressure was required by the kidneys from hypertension-prone animals to excrete a given salt load than by the kidneys of the hypertension-resistant rats.

MECHANISM OF SALT INDUCED HYPERTENSION

It is tempting to make the jump from inherited hypertension-prone rats to humans with essential hypertension. We can formulate the following hypothesis: Many humans are not able to handle large amounts of salt in their diet. The salt habit is of comparatively recent origin in our history. The daily ingestion of large amounts of salt leads to a chronically expanded extracellular volume. The latter acts as a considerable stress on the functional capacity of the kidney and as the individual ages renal competency declines and blood pressure begins to rise. It is the only positive feedback mechanism available to prevent edema. By contrast, the renin-angiotensin mechanism is designed mostly to conserve rather than enhance salt loss. But such a negative feedback mechanism is severely limited as opposed to a positive feedback mechanism which has infinite gain.

An additional facet of this hypothesis is that renal functional capacity to handle an excess volume is not uniformly distributed in the population. It varies from individual to individual as an inherited characteristic. In fact, it is distributed in the same unimodal way that blood pressure is distributed in the population. The individuals who are so unfortunate as to have kidneys with a poor functional capacity to excrete salt are destined to develop hypertension if exposed to a daily intake of salted foods: salt sensitive hypertension. Those with a high functional capacity to excrete salt and water loads will maintain normal diastolic blood pressure throughout their lifetimes: salt resistant hypertension.

EXTRACELLULAR VOLUME. WHAT IS NORMAL?

What is a normal extracellular volume? In the days when the rice and fruit diet (which contains less than 8 mEq of sodium per day) was popular, blood pressure could be reduced in many hypertensive patients for as long as the patients could tolerate the diet. Investigators at that time found that the reduction of blood pressure was associated with a 15% fall in extracellular volume and a 10% decrease in plasma volume [20, 21].

Wilson & Freis [22] found that during treatment with chlorothiazide the fall in blood pressure was associated with a 15% reduction in extracellular volume and a 10% reduction in plasma volume. The agreement with the

rice, no-salt diet was identical. At that time we postulated that there was a readily mobilizable pool of extracellular volume the removal of which led toward normalization of blood pressure. Following thiazides bodily defenses such as the renin-angiotensin system and reduction of blood pressure itself (causing a fall in glomerular filtration rate and possibly other renal changes) prevented a further depletion of extracellular volume with continued treatment with thiazide diuretics.

What is the significance of this mobilizable pool of extracellular volume that is removed by diets very low in sodium or by diuretics and which results in a fall to or toward normal in blood pressure? Probably man in the primitive state did not have such a mobilizable excess of extracellular fluid that we have today because of their very low sodium intakes. If we can judge from the high renin and aldosterone levels of the unacculturated Yanomamo Indians and by their very low salt diets it is likely that they do not have this labile pool of extracellular fluid either. If so, the extracellular and plasma volumes of modern man are chronically expanded 10 to 15% above what nature intended for us to have. This abnormal expansion of extracellular volume provides the stimulus to hypertension in susceptible (salt-sensitive) individuals. The response to this volume expansion is the same that Ledingham, Borst & Guyton observed in their experimental forms of hypertension.

ANCILLARY MECHANISMS

The mechanistic theory of Ledingham is not the only way in which excess volume can induce hypertension. There are, in fact, several other possible mechanisms. The hypertensive response to norepinephrine is enhanced when volume is expanded and is decreased when volume is contracted [23]. Similarly, the response to antihypertensive agents is increased by volume depletion [24]. Therefore, an expanded extracellular and plasma volume tends to raise blood pressure by enhancing the effects of pressor stimuli and diminishing the activity of depressor stimuli.

Another possible enhancing mechanism is resetting of the baroreceptors. If an expansion of volume acts as a pressor stimulus the hypertension will be combatted by the baroreceptors only if the volume stimulus is of relatively short duration. However, if the elevation of blood pressure continues for several days the baroreceptors tend to reset to the higher level of blood pressure [25].

CONCLUSION

There is a close relationship in many individuals between salt-induced volume changes and blood pressure. Firstly, an increase in volume induces a series of hemodynamic changes often leading to hypertension. Secondly, reduction of blood pressure with many antihypertensive drugs, other than diuretics, often lead to salt and water retention. Thirdly, cross-transplantation of the kidneys of a salt sensitive rat into a salt resistant animal results in the development of hypertension in the salt resistant rat. When the kidneys from a salt resistant rat are transplanted into a salt-sensitive animal, the latter becomes normotensive. These experiments indicate that there is an inherited defect which is related to the kidney's intrinsic ability to excrete salt. This defect is present in some individuals (salt sensitive) and not in others. Diuretics act by enhancing the ability of the kidney to excrete excess salt and, thereby, lower blood pressure.

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